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(54) Title of the Invention: An Enteric Coated Soft Capsule

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Specification

1. Title of the Invention

An Enteric Coated Soft Capsule

2. Claims

(1) An enteric coated soft capsule of which a seamless external film formed by a non-gelatin base material comprised of a cross-linked polysaccharide or auxiliary agent thereof is hardened by a divalent higher cation.

(2) An enteric coated soft capsule as described in claim 1 in which the aforementioned cross-linked polysaccharide is sodium alginate.

(3) An enteric coated soft capsule as described in claim 1 in which the aforementioned cross-linked polysaccharide is a low-methoxy pectin.

(4) An enteric coated soft capsule as described in claim 1 in which the aforementioned divalent cation is a calcium ion.

(5) An enteric coated soft capsule as described in claim 1 in which the aforementioned auxiliary agent is a water-soluble polyvalent alcohol.

3. Detailed Description of the Invention

Field of Industrial Use

This invention relates to an enteric coated soft capsule, and, in greater detail, it relates to a non-gelatin enteric coated soft capsule.

Prior Art

Conventionally, soft capsules with a gelatin base agent treated with formalin or capsules coated with an enteric coating substance or soft capsule in which enteric polymer compounds are used as the base agent have been used as enteric coated soft capsules. However, their workability and the properties of the external film have not been satisfactory.

Enteric coated capsules obtained by compounding a lower-methoxy pectin or sodium alginate with a base material comprised of gelatin and a polyvalent alcohol or derivative thereof were disclosed as capsules in which the drawbacks of these enteric coated capsules were eliminated (Japanese Patent Application Early Disclosure No. 58[1983]-172,313.

Problems the Invention Is Intended to Solve

However, because gelatin is used as the base material of these enteric coated capsules, there are severe limitations on the compounding ratio of the lower-methoxy pectin or sodium alginate and the gelatin. In addition to this limitation range, there are such impediments as poor workability, loss of enteric solubility of the external film and decrease of storage stability. In the manufacturing process, the double-solution titration method is used and heat and dissolution of the base material are necessary to seal the core substance into a seamless capsule. The external film of the seamless capsule that is manufactured is sticky and weak and is subject to the action of water when it is in unaltered form. As a result, the external film is immediately cross-linked and

hardened by a cross-linking and hardening solution and the seamless capsule cannot be made enterically soluble. Consequently, if this seamless capsule is not introduced into an oleaginous cooling solution to effect cooling and hardening of the external film and then removed to the outside of the system, it cannot be introduced into the next cross-linking and hardening (enteric coating) process. That is, in the manufacture of this enteric coated soft capsule, there are the drawbacks that it is accompanied by interruption in the operations so that continuous operation cannot be performed consistently, with a reulting increase in manufacturing cost.

Means for Solving the Problems

The inventors conducted intensive research for the purpose of eliminating the drawbacks of this enteric soft capsule. As a result, they perfected this invention by discovering that enteric coated soft capsules of superior properties can be manufactured without interrupting the operations by not using gelatin, which leads to impediments in compounding, and by using a base agent comprised of a cross-linked hardened polysaccharide or auxiliary agent together with it that is cross-linked and hardened by a divalent or higher cation.

The soft capsule of this invention is an enteric coated soft capsule of which the external film, which is formed by a non-gelatin base agent comprised of a cross-linked polysaccharide or an auxiliary agent together with it, is hardened by a divalent or higher cation.

In this invention, the term cross-linked polysaccharide refers to a water-soluble polysaccharide that is cross-linked and hardened by the aforementioned divalent or higher cation. For example, it can be an intercellular polysaccharide, an acidic polysaccharide comprised of α 1 $\rightarrow$ 4 bonds of D-galacturonic acid or salts or derivatives thereof. Preferably, it is a water-soluble salt of alginic acid such as sodium alginate, sodium alginate containing calcium, potassium alginate and ammonium alginate and lower-methoxy pectins of a degree of esterification of 20 to 45%.

The term auxiliary agent refers to an additive for the purpose of improving the properties of the external film of the capsule. It confers plasticity on the external film or controls the speed of enteric dissolution. For example, such agents can include water-soluble polyvalent alcohols, glycerol fatty acid esters, acetylated monoglycerides, phthalic acid esters and citric acid esters. Preferably, they are divalent to hexavalent alcohols such as glycerol, erythritol, arabitol, sorbitol, propylene glycol, polypropylene glycol, ethylene glycol and polyethylene glycol and glycerol fatty acid esters such as acetin, diacetin and triacetin.

The term non-gelatin base agent refers to a base agent that does not contain any gelatin whatsoever. The base agent refers to an aqueous solution of the aforementioned cross-linked polysaccharide or a substance obtained by adding an auxiliary agent to it. As required, commonly used colorants, lubricants and flavor and odor-control agents can be added. The core substance is seamlessly coated with the external film of the seamless soft capsule. It is then

cross-linked and hardened by the divalent or higher cation to be discussed subsequently and changed to an enteric coating film.

The divalent or higher cation is an ion of a metal that can be tolerated physiologically. For example, magnesium, calcium, strontium, barium, iron and aluminum can be used. However, calcium ions are the most desirable.

Compounds that furnish calcium ions can include water-soluble calcium salts such as calcium chloride, calcium acetate, calcium hydroxide, monobasic calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate and calcium lactate. However, calcium chloride is preferable.

In the soft capsule of this invention, the base agent is comprised of an aqueous solution of a suitable concentration of cross-linked polysaccharide or of a suitable quantity of auxiliary agent together with it. For example, with sodium alginate, 1 to 10 weight %, and, preferably, 2 to 6 weight %, of base agent is used, and, with methoxy pectin, 1 to 20 weight %, and, preferably, 10 to 15 weight %, of base agent is used. When an auxiliary agent is used, with less than 10 weight % of base agent, 0.5 to 5 times the weight of cross-linked polysaccharide is used. The base agent is cross-linked and hardened by the cross-linking and hardening agent containing the aforementioned divalent or higher cations, with the enteric soluble film being formed. An aqueous solution that contains 1 to 30%, and, preferably, 5 to 10%, of a compound that furnishes the aforementioned divalent or higher cations is used as the cross-linking and hardening agent.

A base agent comprised only of cross-linked polysaccharide is of good workability and the water resistance of the external film that is obtained is extremely great. Consequently, the thickness of the external film can be increased or decreased and dissolution time in the intestinal tract can be regulated by suitably decreasing or increasing the concentration of the base agent.

The water resistance of an external film obtained with a base agent comprised of cross-linked polysaccharide and auxiliary agent is less than that of one comprised only of cross-linked polysaccharide. Consequently, the dissolution time in the intestinal tract can be regulated by suitably increasing or decreasing the quantity of auxiliary agent added.

The soft capsule of this invention can contain an oleaginous or aqueous core substance.

An oleaginous core substance is prepared by mixing and melting an oleaginous drug (for example, erythromycin, erythromycin ethylsuccinate, erythromycin propionate, erythromycin lactobionate, erythromycin lauryl succinate, pentoxifylline, nitrofurantoin, nicotinoyl antipyrine, aspirin, pyridoxal phosphate, vitamin A oil, retinol acetate, ergocalciferol, tocopherol acetate, riboflavin and nifedipine) with one or a mixture of two or more fats and oils (for example, plant oils such as corn oil, sesame oil, rapeseed [canola] oil, olive oil, palm oil, peanut oil and hardened oil and animal oils such as fish oil, beef tallow, lard and mutton), waxes (for example, carnauba wax, palm wax, sugar cane wax, beeswax, bleached beeswax, wool fat and montan wax) and glycerol neutral

chain fatty acid esters (for example, Sansoft* No. 700P-2 (brand name, monoester, manufactured by Taiyo Chemicals (Ltd.)) and Panasate* 810 (brand name, triester, manufactured by Nippon Oils and Fats (Ltd.)).

Aqueous core substances are prepared by mixing aqueous drugs (for example, potassium choride, Thiola [tiopronin], potassium L-asparaginate, methylcysteine, hexamine mandelate, protoporphyrin sodium, buformin, fradiomycin, chymotrypsin, seaprose S, bromelain, ATP-2Na, FDA, ephedrine chloride, ascorbic acid, thiamine chloride, pyridoxal phosphate and pyridoxine hydrochloride) with aqueous solutions of water-soluble polyvalent alcohols (for example, glycerol, erythritol, sorbitol and polyethylene glycol) and water-soluble cellulose derivatives (for example, hydroxypropylcellulose and carboxymethylcellulose).

The soft capsules of this invention can be manufactured, for example, by the following methods.

(1) Preparation of base agent

A cross-linked polysaccharide or a cross-linked polysaccharide together with an auxiliary agent are weighed out in specified quantities and they are dissolved by adding purified water in small quantities little by little as the mixture is being heated over a hot bath. After a specified temperature has been reached, the solution is cooled to a specified temperature, and, when required, other additives are added and a transparent, viscous base agent is prepared.

(2) Preparation of core substance

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* phonetic spelling—Trans. Note.

←(1) Preparation of oleaginous core substance

Oils and fats, waxes and glycerol neutral-chain fatty acids are weighed out in specified quantities and dissolved while being heated over a hot bath. After the solution has cooled to close to room temperature, a specified quantity of oleaginous drug is added and is mixed or dissolved to a homogeneous state, thus preparing the oleaginous core substance.

↑(2) Preparation of aqueous core substance

Water-soluble polyvalent alcohols and water-soluble cellulose derivatives are weighed out in specified quantities, an amount of four/fifths the required quantity of purified water is added little by little while the mixture is being heated over a hot bath, with the mixture being dissolved, and the viscous liquid that has been produced is cooled to room temperature. A specified quantity of aqueous drug is added to the liquid and is mixed or dissolved to a homogeneous state. The remaining quantity of purified water is added and the aqueous core substance is prepared.

(3) Manufacture of soft capsule

←(1) A seamless soft capsule manufacturing device (for example, the seamless soft capsule manufacturing device Mark II, manufactured by the Globex* Company) which is equipped with a coaxial double nozzle is used.

The base agent is introduced into the nozzle on the outer side of the coaxial double nozzle, the core drug is introduced into the nozzle on the inner

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* phonetic spelling—Trans. Note.

side, the oleaginous vehicle on the lower part (for example, a plant oil such as soybean oil, canola oil or corn oil, a liquid paraffin or a glycerol neutral-chain fatty-acid ester such as Panasate* 810 or Sansoft* 700P02) and the cross-linking/hardening agent are set facing each other in an overlaid double layer and the base agent and the core substance are extruded simultaneously. The oleaginous vehicle and the cross-linking/hardening agent may be maintained at normal temperature, it not being necessary for them to be cooled.

↑(2) When the base agent is of low viscosity, the tip of the aforementioned double-layer nozzle is held above the oleaginous vehicle and the base agent and the core substance are dripped from the tip of the aforementioned double-layer nozzle into the space drop by drop.

The double-layer liquid drops that are produced in the space become essentially spherical during their fall through space and their shape becomes further regulated during their fall into the oleaginous vehicle. When the cross-linking/hardening agent in the bottom layer of the oleaginous vehicle is stirred fairly strongly, the oleaginous vehicle forms a reversed conical shape at the interface of the oleaginous vehicle and the cross-linking/hardening agent and eats into the cross-linking/hardening agent. That is, in the center region, the oleaginous vehicle eddies and dangles, while, in its periphery, the cross-linking/hardening agent rises. As a result of the impetus of falling of the double layer liquid drops and of the suction force of the eddy at the center, [the drops] break through the interface of the oleaginous vehicle and easily move into the cross-linking/hardening agent. (Mode of dropping through air)

→(3) When the base agent is of high viscosity, the tip of the aforementioned double-layer nozzle is immersed in the oleaginous vehicle, the oleaginous vehicle is faced downwards and the base agent and the core substance are fed simultaneously into the oleaginous vehicle from the tip of the aforementioned double-layer nozzle while being refluxed. After this double-layer liquid has been elongated by the flow of the oleaginous vehicle, it is cut and double-layer liquid drops are formed that are adjusted to a spherical shape during their movement through the oleaginous vehicle. When the cross-linking agent in the bottom layer is gently stirred, the same phenomenon as in (2) occurs, the double-layer drops break through the interface of the oleaginous vehicle as a result of the impetus of pushing and of the suction force of the eddy at the center and move into the cross-linking/hardening agent. (Mode of dropping through liquid)

↓(4) The double-layer liquid drops that have moved into the cross-linking/hardening agent as described in paragraphs (2) or (3) are maintained in unaltered form for 1 to 30 minutes, during which time the outer film undergoes cross-linking and hardening. They are then removed and washed with water. In order to prevent deformation, they are dried at a comparatively low temperature (20 to 40°C for 1 to 3 days, and, preferably, for 2 days). The enteric coated soft capsule of this invention of any desired diameter, and, preferably, of diameters of 0.5 to 11 mm can be manufactured by varying the diameter of the coaxial double nozzle or by varying the viscosity of the base agent and the core substance.

For example, when a coaxial double nozzle is used, enteric coated soft capsules of 0.5 to 14 mm in diameter can be obtained by setting the diameter of the inner-side nozzle at 0.5 to 8 mm and the diameter of the outer-side nozzle at 1 to 17 mm.

Action

The soft capsules of this invention have the properties of not dissolving in water and Pharmacopoeia Solution 1 and of dissolving only in Pharmacopoeia Solution 2.

We shall now describe the action of this invention in specific terms by presenting experimental examples.

Experimental Examples

Base agents and core substances were formulated as indicated below. Soft capsules were prepared in accordance with Example 1 or Example 2 using a coaxial double nozzle comprised of an inner-side nozzle with an inside diameter of 2 to 8 mm and an outer-side nozzle of an inside diameter of 7 to 17 mm and the disintegration test of the 10th Revised Edition of the Japanese Pharmacopoeia was performed on these capsules.

The results are shown in the following table.

Formulations

Components (weight %) Test material		1	2	3	4	5	6	7	8	9	10
Base agent	Sodium alginate	3	3.5	4	4.5	5	3	3.5	4	4.5	5
	Glycerol	5	5	5	5	5					
	Water	92	91.5	91	90.5	90	97	96.5	96	95.5	95
	Total	100	100	100	100	100	100	100	100	100	100
Core Substance	Tocopherol acetate	50									
	Soybean oil	40									
	Bleached beeswax	10									
	Total	100									

Disintegration Tests (minutes)

Test solution Test material	1	2	3	4	5	6	7	8	9	10
Pharmacopoeia Solution I	--	--	--	--	--	--	--	--	--	--
Pharmacopoeia Solution II	3	4	4	5	7	4	5	10	14	15

(Note)

- : Did not dissolve in 2 hours.

Effect of the Invention

The soft capsule of this invention not only has the superior enteric dissolution properties of not dissolving within 2 hours in Pharmacopoeia Solution I and of dissolving in a short time in Pharmacopoeia Solution II, but also has wide utility in that it can contain both oleaginous core substances and aqueous core substances.

Further, because the base agent does not contain any gelatin whatsoever, the external film is of superior resistance and can be stored for long periods, there are few restrictions on compounding in manufacture, there is good

workability and continuous operations can be performed until the finished product is prepared without removing the intermediate products to the outside of the system during the course of manufacture. For this reason, manufacturing costs can be markedly decreased.

Consequently, the soft capsules of this invention can be used as enteric coated soft capsules.

Examples

We shall now describe this invention in specific terms by presenting examples.

Example 1

(1) 5 g of sodium alginate were dissolved by adding 95 g of purified water little by little while the material was heated over a hot bath. The solution was then cooled to room temperature, with a base agent being prepared.

(2) 17 g of Panasate* 810, 40 g of Sansoft* No. 700P-2 and 3 g of bleached beeswax were dissolved by heating over a hot bath and the solution was cooled to room temperature, after which 40 g of erythromycin were added, with an oleaginous core substance being prepared.

(3) A seamless soft capsule was manufactured by the dripping method through air using the base agent and oleaginous core substance obtained as described in the foregoing paragraphs (1) and (2), using a seamless soft capsule

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* phonetic spelling—Trans. Note.

manufacturing device Mark II manufactured by the Globex* Company that was equipped with a coaxial double nozzle comprised of an inner-side nozzle of an inside diameter of 1 mm and an outer-side nozzle of an inside diameter of 1.5 mm and using a 5% aqueous solution of calcium chloride as the cross-linking/hardening agent, with cross-linking/hardening time set at 5 minutes.

The hardened soft capsule was removed and was washed in running water. It was then dried for 3 days at 20°C and a soft capsule of 1 mm in diameter was obtained.

Example 2

(1) 2.5 g of sodium alginate, 5 g of glycerol and 5 g of sorbitol were mixed to a homogeneous state and were dissolved by adding 87.5 g of purified water little by little while the mixture was being heated over a hot bath. The solution was then cooled to room temperature, with a base agent being prepared.

(2) An oleaginous core substance was prepared as in Example 1 (2) using 80 g of soybean oil, 20 g of bleached beeswax and 10 g of pyridoxal phosphate.

(3) A seamless soft capsule was manufactured by the into-solution dripping method using the base agent and oleaginous core substance obtained as described in the foregoing paragraphs (1) and (2), using a seamless soft capsule manufacturing device Mark II that was equipped with a coaxial double nozzle comprised of an inner-side nozzle of an inside diameter of 2 mm and an outer-side nozzle of an inside diameter of 8 mm and using liquid paraffin at 20°C as the oleaginous vehicle and a 5% aqueous solution of calcium chloride as the

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* phonetic spelling—Trans. Note.

cross-linking/hardening agent, with cross-linking/hardening time set at 10 minutes.

The hardened soft capsule was removed and was washed in running water. It was then dried for 3 days at 20°C and a soft capsule of 5 mm in diameter was obtained.

Example 3

(Base agent)	
Sodium alginate	2 g
Glycerol	3.5 g
Sorbitol	4 g
Purified water	90.5 g
(Oleaginous core substance)	
Tocopherol acetate	5 g
Soybean oil	40 g
Bleached beeswax	10 g
Retinol acetate	1,000,000 IU

Treatment was performed as in Example 2 using the base agent and oleaginous core substance of the composition described above and a soft capsule of 5 mm in diameter was obtained.

Example 4

(1) (Base agent)

Sodium alginate	3 g
Glycerol	3 g
Sorbitol	3 g
Purified water	91 g

The base agent was prepared as in Example 2 (1).

(2) 5 g of hydroxypropylcellulose and 20 g of glycerol were added and dissolved little by little into 56 g of purified water while being heated over a hot bath. The solution was then cooled to room temperature and a viscous solution was obtained.

50 mg of ephedrine chloride were added to this solution, 14 g of purified water were then added and an aqueous core substance was obtained.

(3) A soft capsule of 4 mm in diameter was obtained as in Example 2 (3) using the base agent and aqueous core substance obtained as described in the foregoing paragraphs (1) and (2) and using a seamless soft capsule manufacturing device Mark II that was equipped with a coaxial double nozzle comprised of an inner-side nozzle of an inside diameter of 2 mm and an outer-side nozzle of an inside diameter of 7 mm.

Example 5

(Base agent)

Sodium alginate	3 g

Glycerol	2 g
Sorbitol	5 g
Purified water	80 g
(Aqueous core substance)	
Ascorbic acid	10 g
Thiamine hydrochloride	2 g
Pyridoxal hydrochloride	0.3 g
Glycerol	20 g
Hydroxypropyl glucose	2 g
Purified water	30 g

A soft capsule of 0.5 mm in diameter was obtained as in Example 2 (3) using the base agent and the aqueous core substance of the compositions described above and using a seamless soft capsule manufacturing device Mark II that was equipped with a coaxial double nozzle comprised of an inner-side nozzle of an inside diameter of 0.5 mm and an outer-side nozzle of an inside diameter of 1 mm.

Example 6

(Base agent)	
Lower-methoxy pectin	10 g
Sorbitol	6 g
Purified water	84 g
(Oleaginous core substance)	

Ergocalciferol	50,000 IU
Tocopherol acetate	0.5 g
Retinol acetate	1,000,000 IU
Riboflavin	1 g
Soybean oil	30 g
Bleached beeswax	10 g

A soft capsule of 14 mm in diameter was obtained as in Example 2 (3) using the base agent and oleaginous core substance of the compositions described above and using a seamless soft capsule manufacturing device Mark II that was equipped with a coaxial double nozzle comprised of an inner-side nozzle of an inside diameter of 10 mm and an outer-side nozzle of an inside diameter of 17 mm.

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